Epithelioid Angiomyolipoma of the Kidney Mimicking Renal Cell Carcinoma: A Clinicopathologic Analysis of Cases and Literature Review

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Classical renal angiomyolipoma (AML) is a common tumor that, in most cases, follows a benign course and has clearly defined radiologic and histological characteristics. However, rare cases of clinically aggressive or malignant AML, the epithelioid variant of AML (EAML), have been reported. Here, we review the five cases of EAML diagnosed since 2000 at our institution to highlight the spectrum of clinical, radiological and histological characteristics. In all cases, renal lesions seen on computed tomography (CT) were considered as suspicious for renal cell carcinoma (RCC) without tumor extension or metastasis. One of the two patients with definitive tuberous sclerosis complex had a small conventional AML with fat content in the other kidney. Histologically, these tumors can resemble sarcomatoid RCC or high grade RCC. The final diagnosis is established by the presence of perivascular epithelioid cells and immunohistochemistry markers. There was no evidence of local recurrence or metastatic disease found by sonography, CT and magnetic resonance imaging during the follow-up period. EAMLs are capable of aggressive or malignant clinical behavior. Approximately one third of the reported EAMLs show advanced disease; therefore, we recommend that it is important to treat and closely follow-up such cases, similar to that for RCC, because of its malignant potential.

Key Words: epithelioid variant, renal angiomyolipoma
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Classic renal angiomyolipoma (AML) is one of the most common benign renal lesions of the kidney, comprising 2.0–6.4% of all renal tumors [1]. In most cases, AML follows a benign course and has clearly defined radiological and histological characteristics. Rare cases of clinically aggressive or malignant AML, which is histologically categorized as epithelioid AML (EAML), have been reported. EAML is highly cellular, composed of atypical epithelioid cells, and has no or a minimal amount of fat tissue, which often resemble renal cell carcinomas (RCC) both radiographically and histologically. We describe five cases of EAML to illustrate the spectrum of clinicopathological features and we review the literature.

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Methods

Between January 2000 and December 2007, five patients were diagnosed with EAML at our institution. All medical records were reviewed and summarized. Renal tumors were staged according to the American Joint Committee on Cancer staging manual. Preoperative staging evaluation included computed tomography (CT) of the abdomen/pelvis, chest X-rays and a complete metabolic profile. Table 1 lists the antibodies used for the immunohistochemical analysis. Immunohistochemical analysis was performed using appropriate positive and negative controls. Formalin-fixed, paraffin-embedded samples were stained by immunohistochemistry using the avidin-biotin-peroxidase complex.

Results

Table 2 summarizes the patient characteristics. All five patients had isolated heterogeneous renal masses

Table 1. Antibodies used for immunohistochemical analysis

Antibody	Clone	Dilution	Pretreatment	Source
Melanoma	Monoclonal HMB-45	1:100	None	Biogenex
Cytokeratin	Monoclonal AE1/AE3	1:50	Heat—5 min	Dako
S100	Polyclonal	1:1,600	Trysin—10 min	Dako
Smooth muscle actin	Monoclonal 1A4	1:50	None	Biogenex
Muscle actin	Monoclonal HHF-35	1:100	None	Dako

Table 2. Clinical characteristics of patients diagnosed with epithelioid angiomyolipoma

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (yr)	42	32	52	37	35
Sex	Female	Male	Female	Male	Male
TSC	Yes	No	Yes	No	No
Renal lesion					
Symptomatic	No	Yes*	No	No	No
Size	5 cm	7.3 cm	3 cm	2.6 cm	6.8 cm
Location	Left low	Left middle	Right middle	Left lower	Left upper
Fat densities (CT finding)	No	No	No†	No	No
Necrosis	No	Yes	No	No	No
Hemorrhage	Yes	Yes	No	No	No
Tumor thrombus	No	No	No	No	No
Local advance or distal metastasis	No	No	No	No	No
Lymph node adenopathy	No	No	No	No	No
Surgical procedure	Nephrectomy	Nephrectomy	Laparoscopic partial nephrectomy	Nephrectomy	Nephrectomy
TNM stage	T1bN0M0	T2aN0M0	T1aN0M0	T1aN0M0	T1bN0M0
Immunohistochemistry					
HMB-45	Positive	Positive	Positive	Positive	Positive
Cytokeratin	Negative	Negative	Negative	Negative	Negative
S100	Negative	Negative	Negative	Negative	Negative
Time to recurrence/length of follow-up (mo)	–/80	–/36	–/1‡	–/1	–/11
Status	Alive	Alive	Lost to follow-up	Alive	Alive

*Symptoms resulted from hemorrhage into a 7.3 cm renal lesion; †she had a small conventional angiomyolipoma with fat content on the other side of kidney; ‡we lost follow-up for case 3 who had bilateral renal AML because she moved to a foreign country.

noted on CT scan. None of the lesions contained fat components (<–20 HU) or calcification (Figure 1), but one lesion showed central hemorrhage and necrosis (Case 2). There were no instances of lymphadenopathy or venous invasion. These masses showed good enhancement in the post-contrast arterial portal phase. One (Case 3) of the two patients with definitive tuberous sclerosis complex (TSC) had a small conventional AML with fat content in the other kidney (Figure 2). Because all of the lesions were considered as suspicious for RCC, all of the patients received surgical intervention (radical or partial nephrectomy with/without laparoscopic method) and close follow-up (1–80 months). No patient had local recurrence or distal metastasis on sonography, CT and magnetic resonance imaging (MRI) during the follow-up period. Because the tumor lesion of Case 3 who had stage 3 chronic kidney disease and bilateral renal AML had a diameter of less than 4 cm and the peripheral location was without advanced invasion, we performed nephron-sparing surgery with laparoscopic partial nephrectomy. However, she went abroad and was lost to follow-up 1 month after surgery.

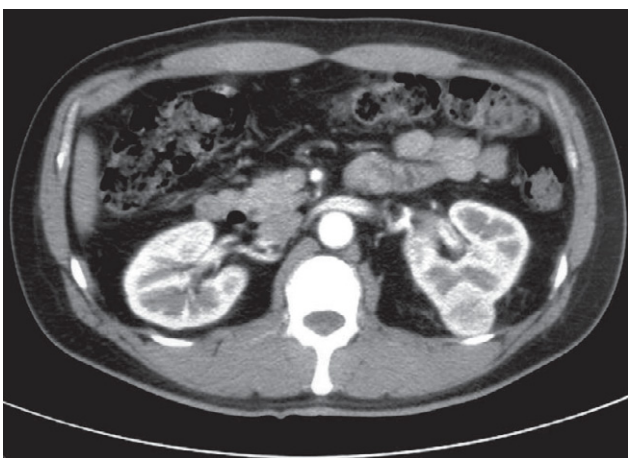

Figure 1. *Case 4. A 2.9 × 2.7 × 3.3 cm slightly hypodense and mildly hypervascular nodule was noted, bulging outward from the left renal parenchyma. The left renal tumor was noted accidentally by sonography during a health check-up.*

The histological diagnosis of these renal tumors was EAML based on microscopic findings and immunohistochemical markers. On the cut surface, the tumors showed a brown and friable extent from the renal parenchyma with or without focal necrosis (Figure 3A). Proliferation of epithelioid cells (PEC) with abundant granular cytoplasm was noted (Figure 3B) in all cases on microscopic examination. These tumor cells had enlarged vesicular nuclei and prominent nucleoli with nuclear anaplasia and mitotic appearance. The main differential diagnoses based on histological characteristics included sarcomatoid RCC, high grade RCC, metastatic melanoma and EAML. Therefore, we used immunohistochemical markers to rule out RCC and melanoma; the absence of staining for epithelial markers such as cytokeratin made RCC unlikely (Figure 3C). We also ruled out melanoma because of negative staining for melanoma markers such as S100. The final diagnosis was confirmed by positive

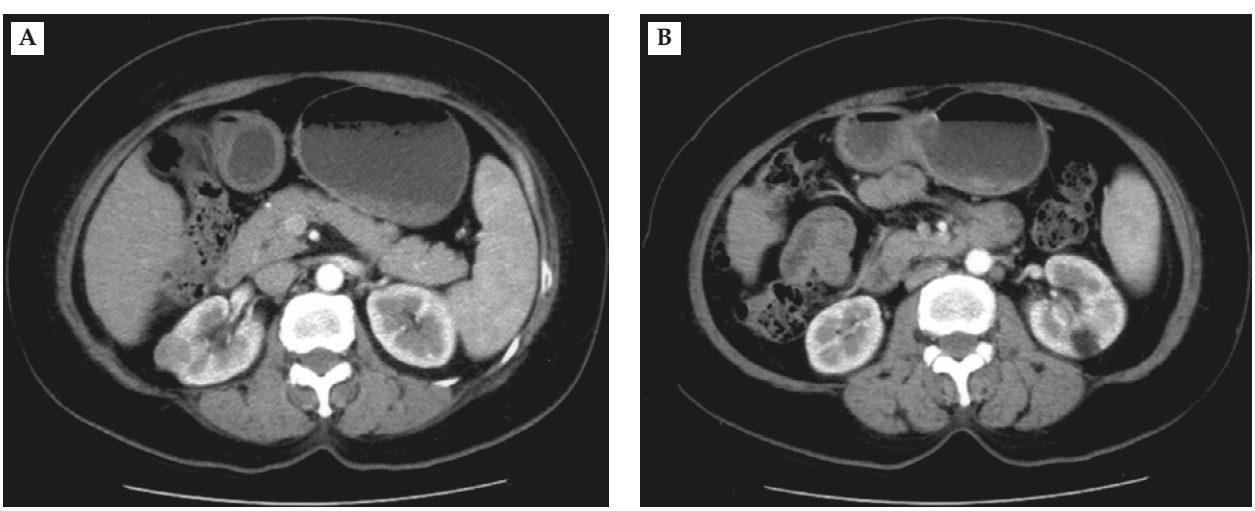

Figure 2. *Computed tomography scan of a patient with tuberous sclerosis complex (Case 3). (A) An enhanced right renal mass devoid of fat densities and considered suspicious for renal cell carcinoma. (B) The renal lesion in the left kidney was characterized by conventional angiomyolipomas.*

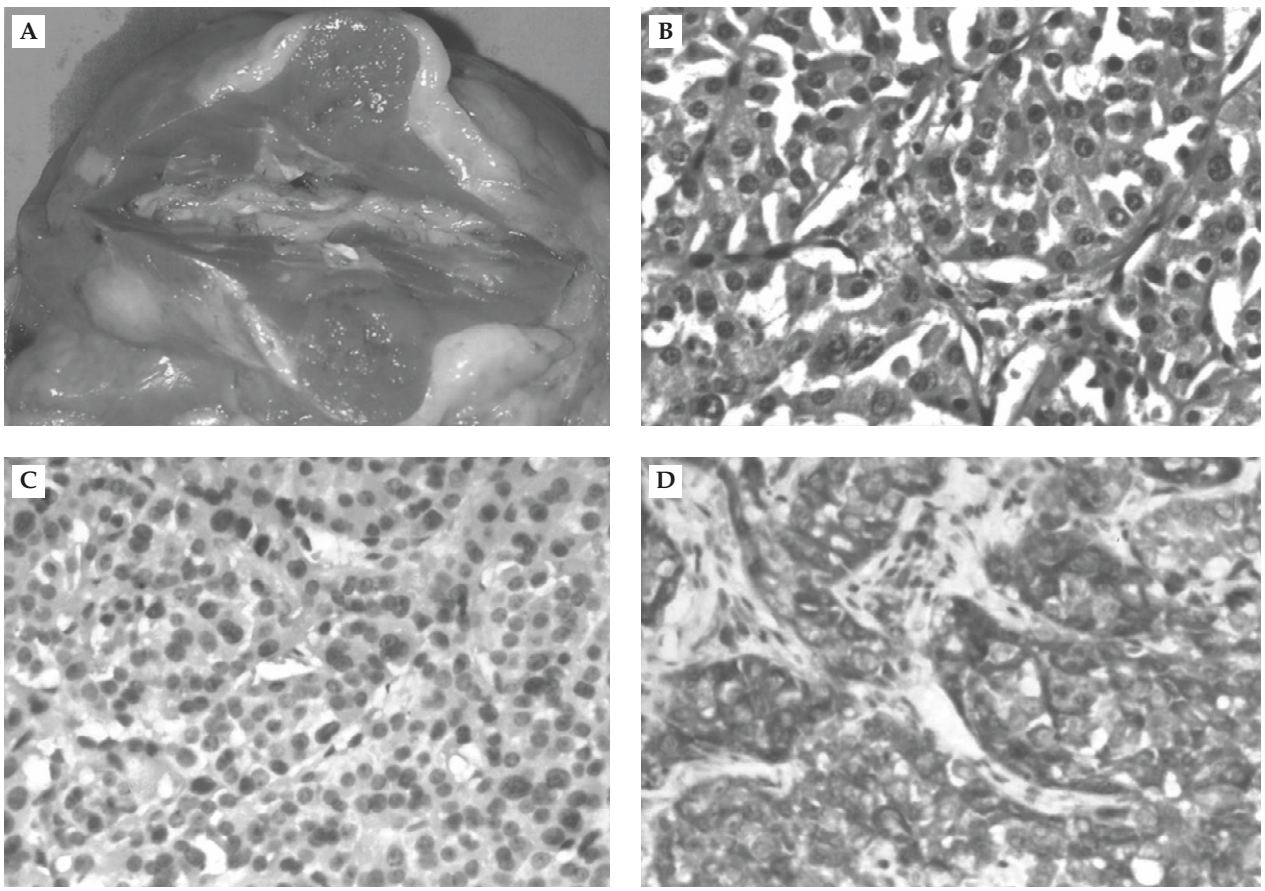

Figure 3. *Case 4. (A) The gross cut surface of the tumors showed a brown and friable extent from the renal parenchyma. (B) Epithelioid angiomyolipoma (AML) is distinguished from conventional AML by the presence of highly cellular and large epithelioid cells, which have abundant eosinophilic cytoplasm (hematoxylin & eosin). (C) Neoplastic cells show no cytoplasmic immunoreactivity to cytokeratin. (D) Neoplastic cells show strong cytoplasmic granular immunoreactivity to HMB-45.*

staining for smooth muscle actin (SMA) and monoclonal HMB-45 (Figure 3D).

Discussion

Typical AML comprises a mixture of mature adipose tissue, smooth muscle cells and thick-walled blood vessels. The components of AML are thought to arise from unsuppressed and aberrant differentiation of renal mesenchyme, belonging to the group of PEComas, tumors derived from perivascular epithelioid cells. In 1996, Zamboni et al proposed a modulation scheme encompassing the morphologic-immunophenotypic variability in tumors composed of PEC, including AML, lymphangioleiomyomas, and clear cell "sugar" tumors of the lung and pancreas [2]. AML can occur as an isolated renal lesion, being solitary and large, or as part of hereditary diseases, most commonly TSC, and are then often small, bilateral and multifocal [3]. Although approximately 50% of patients with TSC develop AML, 90% of renal AMLs are sporadic and unrelated to TSC [4].

Renal AMLs have clearly defined radiological and histological characteristics. On unenhanced CT, lesions with low fat and no calcification are diagnostic for AML [5], and we recommend an algorithm for radiological diagnosis (Figure 4). MRI is useful when other imaging is equivocal or for evaluation during pregnancy. It is sometimes difficult to differentiate AML with minimal fat from RCC. Kim et al identified some characteristics specific of AML with minimal fat, including homogeneous enhancement, prolonged enhancement pattern, high tumor attenuation on unenhanced scans and less mean enhancement [6]. The diagnosis of AML can usually be established by imaging alone, but CT-guided percutaneous biopsy (2–5 cores), which has a high diagnostic accuracy in

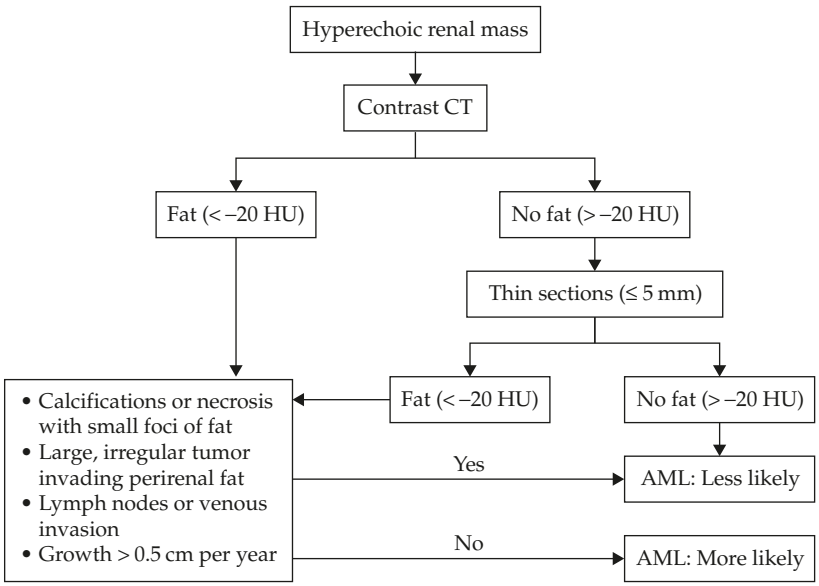

Figure 4. *An algorithm for radiological diagnosis of renal angiomyolipoma.*

predicting malignancy, is sometimes necessary if RCC is suspected, particularly for small renal tumors of less than 4 cm in size [5,7].

In most cases, AML is asymptomatic and follows a benign course. However, rare cases of clinically aggressive or malignant AML have been reported. These atypical variants of AML are histologically categorized as EAML. We review the case series (more than 2 patients) of EAML since 1998 in Table 3 [3,8–12]. There are 22 patients in this summary and most of them have no fat components in the image survey. All EAMLs were positive for melanoma markers (HMB-45). The rate of metastasis or recurrence seems to be directly proportional to the size of the primary renal mass. Approximately one third of patients with EAML present with extension into the perirenal soft tissue and vena cava, and local recurrence and distant metastasis, such as lymph node, lung, liver or spinal cord metastasis [3,13,14]. However, it is important to recognize that EAML can develop adjacent to or even within conventional AML [12,15].

EAML often resembles sarcomatoid RCC or high-grade RCC both radiographically and histologically. Under gross examination, EAML usually shows a brown and friable extent from the renal parenchyma with or without focal necrosis. On the other hand, conventional RCC usually has a bright yellow cut surface. Histologically, EAML is solid, highly cellular, with occasional microcysts, composed of medium to large epithelioid cells with clear or eosinophilic cytoplasm. There are also some short spindle cells and numerous giant multinucleated cells [16]. Adipose tissue, smooth muscle and thick-walled vascular elements are usually absent in EAMLs. We were unable to find any reports related to EAML with fat densities noted on CT or MRI. Pea et al reviewed five tumors that were previously reported as RCC in patients with TSC, and three of the tumors were reclassified as EAML. Their study suggests that the increased incidence of RCC associated with TSC may be due to incorrect classification of EAML as RCC [9]. Therefore, further studies are needed to determine the true incidence of EAML; however, five cases of EAML were diagnosed at our institution during an 84-month period, suggesting that EAML is not uncommon. Approximately half of published cases of EAML have a history of TSC [1]; therefore, diagnosis of EAML should be considered in patients diagnosed with sarcomatoid RCC, particularly if the patient has clinical stigmata of TSC.

Because EAML can resemble sarcomatoid RCC and metastatic melanoma, the final diagnosis is established based on the presence of immunohistochemistry markers. Immunoreactivity for HMB-45 antigen, a melanosome-associated protein, has been demonstrated in renal AML. The recognition that AML is uniformly positive for melanoma markers (HMB-45 and melan-A) and smooth muscle markers (HHF-35, SMA and caldesmon) has facilitated correct diagnosis [17]. Of note, all renal AMLs were negative for S100 and cytokeratin. As a classic AML, most EAMLs

Table 3. Summary of clinically reported epitheliod variant of angiomyolipoma in contemporary surgical series

Authors	No. of patients	TSC (+/−/NA)	Nephrectomy/ partial nephrectomy	Size of renal mass (cm, range)	HMB-45 (+/−)	Fat component in image (+/−/NA)	Follow-up (mo, range)	Metastasis or recurrence (+/−)	Status (AWD/ DOD/NED)
Park et al [3]	4	1/3/0	2/2	1.4–17	4/0	0/4/0	4–16	2/2	4/0/0
Bernardini et al [8]	2	0/2/0	2/0	2–3	2/0	0/2/0	14–16	0/2	2/0/0
Pea et al [9]	3	3/0/0	3/0	NA	3/0	0/3/0	NA-18	2/1	0/2/1
Belanger et al [10]	3	0/0/3	3/0	10–12	3/0	0/3/0	NA-24	3/0	1/2/0
Martignoni et al [11]	3	0/3/0	3/0	6–10	3/0	0/3/0	10–84	1/2	2/1/0
Takahashi et al [12]	2	0/0/2	2/0	8–20	2/0	0/0/2	18–60	2/0	1/1/0
Our report	5	2/3/0	4/1	2.6–7.3	5/0	0/5/0	1–80	0/5	4/0/1
Total	22	6/11/5	19/3	NA	22/0	0/20/2	NA	10/12	14/6/2

NA = not available; DOD = died of disease; AWD = alive with disease; NED = no evidence of disease following surgery/treatment.

have the same immunohistochemistry characteristics. Therefore, the histological diagnosis of EAML can be confirmed by evaluating the expression of immunohistochemical marker.

Approximately one third of EAMLs present with aggressive behavior or metastasis; therefore, surgical resection has become the gold standard therapy for localized EAML. Nevertheless, it is important to continue to follow-up the cases after surgery, as for RCC. However, as mentioned above, EAML is part of the perivascular epithelioid cell tumors (PEComa) family and is considered chemosensitive. Metastatic EAML has been treated with a variety of chemotherapeutic agents including doxorubicin, dacarbazine, ifosfamide, cyclophosphamide and cisplatin [3]. However, long-term efficacy and the most effective agent remain to be determined. Surgery seems to yield beneficial outcomes for aggressive EAML [2]. Further studies in this regard and long-term follow-up of patients after surgery will help establish a standard for treatment and follow-up.

EAMLs may occur sporadically or as part of TSC. They often resemble RCC radiographically and histologically, and can be locally aggressive and metastatic. These tumors are distinguished from RCC not only by identifying epithelioid cells within the tumor, but also by immunostaining (positive for HMB45 and negative for cytokeratin and S100). Because approximately one third of cases of EAML show advanced disease, it is essential to initiate appropriate treatment with close follow-up, as for RCC, owing to its malignant potential.

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與腎細胞癌相似之類上皮腎臟血管肌肉脂肪瘤 — 病例分析回顧

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典型腎臟血管肌肉脂肪瘤為常見腫瘤，大多呈現良性病灶且有典型影像及病理學特徵。但少數類上皮腎臟血管肌肉脂肪瘤於臨床有惡性表現。我們回顧自 2000 年以來在高雄醫學大學附設中和紀念醫院中所診斷的五位類上皮腎臟血管肌肉脂肪瘤病例。所有病人經電腦斷層掃描均被診斷為腎細胞癌且沒有其他系統性的轉移。組織切片的結果顯示腫瘤細胞與高度未分化惡性肉瘤腎細胞癌相似。最終診斷依靠發現類上皮細胞的存在及免疫組織化學的標示。手術後在持續追蹤之下，並沒有疾病復發。類上皮腎臟血管肌肉脂肪瘤可能於臨床有惡性表現。此種腫瘤須靠組織切片的成像及免疫組織化學的標示來與惡性腎細胞癌作鑑別診斷。經統計近三分之一的類上皮腎臟血管肌肉脂肪瘤有有惡性表現，故對於此種腫瘤所採取的治療及追蹤方式應和腎細胞癌相似。

關鍵詞：類上皮變化，腎臟血管肌肉脂肪瘤

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